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# Familial risks of Tourette syndrome and chronic tic disorders : a population-based cohort study

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**Familial Risks of Tourette Syndrome and Chronic Tic Disorders. A Population-Based Cohort Study. Allergy. JAMA Psychiatry 2015 Aug;72(8):787-93.**

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Supplementary Materials

## **Familial risks of Tourette Syndrome and Chronic Tic Disorders:**

### **A population-based cohort study**

David Mataix-Cols, PhD<sup>1</sup>, Kayoko Isomura, MD, PhD<sup>1</sup>, Ana Pérez-Vigil, MD<sup>1</sup>, Zheng Chang, PhD<sup>2</sup>, Christian Rück, MD, PhD<sup>1</sup>, K. Johan Larsson, MD<sup>1</sup>, James F. Leckman, MD, PhD<sup>3</sup>, Eva Serlachius, MD, PhD<sup>1</sup>, Henrik Larsson, PhD<sup>2</sup>, Paul Lichtenstein, PhD<sup>2</sup>

<sup>1</sup>Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.

<sup>2</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

<sup>3</sup>Child Study Center and the Departments of Psychiatry, Pediatrics and Psychology, Yale University, New

Haven, CT, USA

Correspondence:

Professor David Mataix-Cols, PhD

Karolinska Institutet

Department of Clinical Neuroscience

Child and Adolescent Psychiatry Research Center

Gävlegatan 22 (Entré B), floor 8

SE-11330 Stockholm

+46 (0)851452207

[david.mataix.cols@ki.se](mailto:david.mataix.cols@ki.se)

Running title: Familial risks of Chronic Tic Disorders

33    **ABSTRACT**

34    **Importance:** Chronic Tic Disorders (CTD), including Tourette Syndrome (TS), are assumed to  
35    be strongly familial and heritable. While gene-searching efforts are well underway, precise  
36    estimates of familial risk and heritability are lacking. Previous controlled family studies were  
37    small and typically conducted within specialist clinics, resulting in potential ascertainment biases.  
38    They were also underpowered to disentangle genetic from environmental factors contributing to  
39    the observed familiarity. Twin studies have been either very small or based on parent-reported  
40    tics in population-based (non-clinical) twin samples.

41    **Objective:** To provide unbiased estimates of familial risk and heritability of TS/CTD at the  
42    population level.

43    **Design and Setting:** Population cohort, multigenerational, family study.

44    **Participants:** Using a validated algorithm, we identified 4,826 individuals diagnosed with  
45    TS/CTD (76% male) in the Swedish National Patient Register between 1969-2009.

46    **Main outcome measure:** Risks (Odds Ratios; OR) for TS/CTD in all biological relatives of  
47    probands, compared to relatives of unaffected individuals (matched on a 1:10 ratio) from the  
48    general population. Structural equation modeling was used to estimate the heritability of  
49    TS/CTD.

50    **Results:** The risk for TS/CTD amongst relatives of TS/CTD probands increased proportionally  
51    to the degree of genetic relatedness. The risks for first-degree relatives (OR= 18.69, 95% CI  
52    14.53-24.05) were significantly higher than for second-degree relatives (OR= 4.58, 95% CI  
53    3.22-6.52) and third-degree relatives (OR= 3.07, 95% CI 2.08-4.51). First-degree relatives at  
54    similar genetic distances (e.g. parents, siblings, offspring) had similar risks for TS/CTD, despite  
55    different degrees of shared environment. The risks for full siblings (50% genetic similarity; OR=  
56    17.68, 95% CI 12.90-24.23) were significantly higher than that for maternal-half siblings (25%  
57    genetic similarity; OR= 4.41, 95% CI 2.24-8.67), despite similar environmental exposures. The

58 heritability of TS/CTD was estimated to be 0.77 (95% CI 0.70-0.85). There were no differences  
59 in familial risk or heritability between male and female patients.

60

61 ***Conclusions and relevance:*** TS/CTD clusters in families primarily due to genetic factors and  
62 appears to be amongst the most heritable neuropsychiatric conditions.

63

64 **Keywords:** Tourette syndrome, Chronic Tic Disorders, family study, genetic epidemiology

## 65 INTRODUCTION

66 Tourette Syndrome (TS) is thought to be a strongly familial and heritable neuropsychiatric  
67 disorder <sup>1</sup>. Controlled family studies have reported a 10- to 100-fold increase in the rates of TS  
68 in first-degree relatives of affected individuals, compared to control relatives <sup>2-6</sup>. Furthermore,  
69 chronic tic disorders (CTD) also occur more frequently among first-degree relatives of TS  
70 probands, compared to relatives of controls (7- to 22-fold increase), suggesting that TS and CTD  
71 share common etiological factors <sup>1</sup>. These previous family studies were carefully conducted but  
72 also had important limitations. First, the estimates of family risk have varied broadly, suggesting  
73 that previous studies may have been underpowered to provide precise estimates of familial  
74 transmission. Second, families were primarily recruited from specialist clinics, potentially  
75 resulting in the inclusion of more severe and impaired cases. Families with several affected  
76 members may have been more likely to volunteer for participation, thus inflating the familial  
77 risk. These possible biases can optimally be addressed by examining the familial structure of  
78 TS/CTD at the population level <sup>7</sup>, recruiting patients from non-specialist clinics and randomly  
79 selecting control families from the general population. Third, studies conducted to date were  
80 underpowered to calculate risks for relatives with different degrees of genetic relatedness to the  
81 proband and different degrees of shared environmental exposures. Consequently, these studies  
82 could not disentangle genetic from environmental factors contributing to the observed familiarity  
83 of TS/CTD. Fourth, previous family studies were too small to examine possible gender

84 differences in familiarity and heritability; this is of critical importance given that TS/CTD is  
85 much more common in males than in females<sup>8-12</sup>.

86 Twin studies are ideal to disentangle these aetiological factors, based on the different  
87 genetic resemblance of twins. To our knowledge, only two small twin studies of diagnosed  
88 TS/CTD cases have been published to date. Price and colleagues<sup>13</sup> recruited 30 identical  
89 (monozygotic (MZ)) and 13 same-sex non-identical (dizygotic (DZ)) twin pairs (mean age 18  
90 years) from the Tourette Syndrome Association and found that 77% of MZ twins and 23% of  
91 DZ twins were concordant for tic disorders (TS or CTD). The MZ concordance rate reached  
92 100% for TS or CTD when direct observational interviews were conducted on the same twin  
93 sample<sup>14</sup>. In another study of 16 pairs of MZ twins (mean age 13 years), 56% were concordant  
94 for TS and 94% were concordant for tic disorders but, because DZ twins were not included, no  
95 conclusions could be made about heritability<sup>15</sup>. Though the higher MZ concordance rates have  
96 been interpreted as implicating genetic factors as strongly contributing to the aetiology and  
97 familial transmission of TS/CTD, and gene-searching efforts are well underway<sup>16-18</sup>, this  
98 evidence comes from small samples that may not represent broader TS and chronic tic  
99 populations.

100 Three recent population-based studies have examined the heritability of parent-rated  
101 tics in children, resulting in modest heritability estimates. A Japanese study of 1896 twin pairs  
102 aged 3-15 (mean 11 years) reported modest heritability estimates (around 30%) for parent-rated

tics<sup>19</sup>. A British study including 854 pairs of 6-year old twins found evidence for strong familial effects on parent-rated tics (61%) but was unable to separate genetic from shared environmental sources of familial aggregation due to power issues<sup>20</sup>. A large nationally-representative sample of over 10,000 Swedish twins aged 9-12, reported heritability estimates for parent-rated tics of 56% [95% confidence intervals (CIs) 37-68], with the remaining variance due to non-shared environmental factors<sup>21</sup>. Although the assessment instrument varied across these studies, collectively, they suggest moderate heritability of parent-rated tics in young people, but it is unclear to what extent these findings can be extrapolated to clinically diagnosed tic disorders.

In an attempt to overcome some of these limitations and provide unbiased estimates of family clustering and heritability of TS/CTD at the population level, we linked and analyzed data from two Swedish population-based registers and tested three hypotheses: 1) TS/CTD will cluster in families at the population level; 2) the risk of TS/CTD will increase proportionally to the degree of genetic relatedness to the proband; 3) shared environment effects will be negligible. In exploratory analyses, we also examined possible gender differences in the patterns of familial clustering of TS/CTD.



## 122    **METHODS**

### 123    *Swedish registers*

124    Following approval from the Regional Ethics Committee in Stockholm, we linked two Swedish  
125    national registers, using the individual national registration numbers assigned at birth.

126            The Multi-Generation Register contains information about the identity of biological  
127    and adoptive parents of each individual born in Sweden since 1932 (with the mother as  
128    informant) or who immigrated to Sweden together with one or both parents before the age of 18  
129    years and lived in Sweden at any time since 1961. Unless the biological/adoptive parents have  
130    actually lived in Sweden since 1947, when the national personal identification number was  
131    introduced, it is not possible to identify them. The father was defined either as the mother's  
132    husband at the time of birth, or the man acknowledged as father by unmarried mothers. With  
133    information on parents, it is possible to create family pedigrees for all individuals with relatives  
134    at increasing genetic and environmental distances from each index person.

135            The National Patient Register contains diagnostic information about patients treated in  
136    Sweden since 1969, with each consultation as a unique record in the register. Initially, it  
137    contained information on all inpatient care. From 2001, however, it also includes individuals  
138    with outpatient visits to specialist physicians (other than general practitioners) that resulted in  
139    one or more diagnoses according to the ICD-10<sup>22</sup>.

140

141 *ICD diagnostic codes*

142 The ICD codes for TS/CTD have been validated in Sweden (Rück et al, submitted). Briefly, we  
143 obtained a random sample of TS/CTD patient records from 3 Swedish counties (N=73), of  
144 which 64 contained sufficient information for analysis. Each file was carefully reviewed and  
145 blindly rated by two independent physicians. There was 100% of agreement between the two  
146 raters regarding the presence or absence of a chronic tic disorder (Kappa = 1,  $p < 0.001$ ). Overall,  
147 the ICD codes had excellent validity, with a positive predictive value (PPV) of 92% for both  
148 raters. The PPVs for ICD-8, ICD-9 and ICD-10 cases were 0.89, 0.86 and 0.97, respectively.

149 Further examination of specific ICD-10 sub-codes, revealed that the majority of  
150 patients who had F95.1 (CTD) codes in the register were diagnosed as TS (F95.2) by the raters  
151 (both motor and vocal tics were identified in the clinical histories). Unspecified tic disorder  
152 (F95.9) cases were diagnosed by the raters as either TS (F95.2), CTD (F95.1), unspecified tic  
153 disorder (F95.9) or transient tics (F95.0), suggesting that F95.9 is used more freely by clinicians.  
154 Consequently, we developed an algorithm to ensure that individuals who had transient tics as  
155 their only or final diagnostic code within the same year of the initial diagnosis were excluded  
156 from the analyses. Furthermore, individuals who received an initial diagnosis of transient, 'other'  
157 or unspecified tics were only included if they received at least an additional diagnosis of a tic  
158 disorder, except if the last available diagnosis was of transient tic disorder given within the same  
159 year of the initial diagnosis (Rück et al, submitted). We did not exclude any participants based

160 on comorbidities, as we preferred not to make assumptions about the hierarchical structure of  
161 mental disorders.

162

### 163 *Data Analyses*

164 The risk of TS/CTD in relatives of probands with TS/CTD were compared with the risk in  
165 relatives of 10 randomly selected, unaffected control individuals matched by sex, birth year and  
166 county of residence at the time of the first recorded TS/CTD diagnosis of the proband. Relatives  
167 were also matched by sex and birth year. For instance, for each proband, we detected all possible  
168 proband-full sibling pairs, and randomly selected 10 control-full sibling pairs matched to  
169 probands-sibling pairs by sex and birth year. Because each proband may appear multiple times  
170 in different categories (e.g. parent, sibling and cousin) depending on family structure, the  
171 matching was done separately for each proband-relative pair to ensure adequate control of  
172 cohort/period effects and allow for equal time at risk for proband-relatives and control-relatives.  
173 The matching procedure was used for all available first-, second- and third degree relatives of  
174 each proband. We also examined potential gender effects by separately analyzing respective  
175 pairs of male-male, male-female, female-female and female-male probands and relatives.

176       Because the data were matched and the outcome dichotomous, we employed a  
177 conditional logistic regression model with the PROC PHREG procedure in SAS, version 9.3<sup>23</sup>.  
178 Because several possibly correlated pairs of relatives from every family could be included in the

179 analysis, we adjusted for the non-independence of family members (e.g. several sibling pairs,  
180 which share the same parents) by computing corrected (less narrow) confidence intervals with a  
181 robust sandwich estimator (covsandwich option in PHREG).

182 By assuming that a continuous normally distributed liability underlies the observed  
183 dichotomous diagnosis of TS/CTD, the tetrachoric correlations of TS/CTD between family  
184 members can be estimated. These are often employed in twin and family studies to obtain  
185 approximate heritability estimates using structural equation modeling. We fitted  
186 liability-threshold models using full siblings and maternal half-siblings to decompose the  
187 variance in liability of TS/CTD into additive genetic effects (A), shared environmental effects  
188 (C), and non-shared environmental effects (E). Age and sex were adjusted for in the threshold of  
189 TS/CTD. The genetic correlation was fixed to 0.5 for full siblings (they share on average 50% of  
190 their segregating genes), and to 0.25 for maternal half-siblings (sharing 25% of their genes), and  
191 we assumed that the family environment is shared between full siblings and maternal  
192 half-siblings (Supplementary Materials). We began our model fitting with a full ACE model  
193 allowing sex difference for the estimates of ACE. We then sought to simplify the model by  
194 equating the ACE estimates between males and females, and then dropped the shared  
195 environmental effects. Goodness of fit between the different models was assessed by a  
196 likelihood-ratio test. Maximum likelihood estimation and univariate model fitting were  
197 performed using the structural equation modeling package OpenMx in R.

198

## 199   **RESULTS**

### 200   *Sample characteristics*

201   Our algorithm resulted in the identification of 4,826 individuals diagnosed with TS/CTD (3,678  
202   or 76.2% male; age mode = 10) between 1969-2009. Of the TS/CTD subjects, 73% had at least  
203   one lifetime psychiatric comorbidity (Attention Deficit Hyperactivity Disorder 38%,  
204   Obsessive-Compulsive Disorder 15%, Pervasive Developmental Disorders [PDD] 20%, Mental  
205   Retardation [MR] 21%, Depression 16%, Anxiety disorders 12%, Other neurotic, stress-related  
206   and somatoform disorders 14%, Substance use 10%).

207

### 208   *Familial risk of TS/CTD*

209   First-degree relatives of individuals with TS/CTD had significantly higher risk of having  
210   TS/CTD than second-relatives and third-degree relatives. In turn, the odds ratios (ORs) for  
211   second-degree relatives were higher than for third-degree relatives, though the confidence  
212   intervals overlapped (**Table 1** and **Figure 1**). The pattern of results did not change substantially  
213   when cases with PDD or MR were excluded from the analyses (Supplemental Figure 1).

214           Shared environmental influences on TS/CTD appeared to be considerably less  
215   important. Full siblings, parents, and children of TS/CTD probands (all with 50% genetic  
216   similarity but siblings assumed to have more shared environment as they grew up together in the

217 same family approximately during the same period of time) had comparable risks. Additionally,  
218 the risks for full siblings (50% genetic similarity) were significantly higher than that for  
219 maternal-half siblings (25% genetic similarity), despite similar shared environmental exposures.  
220 Furthermore, the risks did not differ significantly between maternal and paternal half-siblings  
221 (both with 25% genetic similarity but with maternal half-siblings sharing more environment as  
222 the vast majority (90%) of children in Sweden continue to live with their mother after parental  
223 divorce or separation; Supplementary Materials)<sup>25</sup>. Finally, first cousins (12.5% genetic  
224 similarity) had a 3-fold higher risk of having TS/CTD compared to controls, despite no or  
225 marginal shared environmental exposures with the TS/CTD proband.

226

#### 227 *Gender effects*

228 Analyses by gender of the proband and gender of the relative revealed a higher number of  
229 male-male dyads, but the risks and tetrachoric correlations (which are not affected by sample  
230 size) were approximately similar for male-male, male-female, female-male and female-female  
231 dyads (**Table 2**).

232

#### 233 *Heritability estimates*

234 Tetrachoric correlations were approximately double for full siblings than for maternal  
235 half-siblings (**Table 1**). There was no evidence of quantitative sex differences in the liability to

236 TS/CTD. In the full ACE model, the variance in liability of TS/CTD was largely attributable to  
237 additive genetic factors (0.72, 95% CI 0.42-1.00]), with negligible effect of shared environment  
238 (0.03, 95% CI 0.00-0.16]. The remaining variance was attributable to non-shared environmental  
239 influences and measurement error (0.25, 95% CI 0.08-0.43]. The best fitting model included  
240 additive genetic factors (0.77, 95% CI 0.70-0.85) and non-shared environmental factors (0.23,  
241 0.15-0.30). The shared environment component could be dropped without any significant loss of  
242 fit (**Table 3**).

243

## 244 **DISCUSSION**

245 Extending previous, much smaller, family studies primarily conducted in specialist clinical  
246 settings, TS/CTD was significantly more prevalent among biological relatives of TS/CTD  
247 probands than in relatives of matched population controls. Further, the risk of TS/CTD in  
248 relatives increased significantly with increasing genetic relatedness to the proband. The pattern  
249 of results was similar in male and female patients. The heritability of TS/CTD was estimated to  
250 be approximately 77%, with the remaining variance being attributable to non-shared  
251 environmental influences and measurement error.

252       Together with the previous family and twin literature, largely derived from clinical  
253 samples of European origin, our data confirm that TS/CTD runs in families primarily due to  
254 genetic factors. Previous twin studies of strictly diagnosed TS/CTD<sup>13,15</sup> were too small to  
255 provide robust heritability estimates, whereas population-based (non-clinical) studies of

256 parent-rated tics <sup>19-21</sup> estimated the genetic contribution to range between 30-60% but were  
257 limited by the lack of clinician-based diagnostic assessments. Recent efforts to estimate the  
258 heritability of TS from genotyped data employing genome-wide complex trait analysis methods  
259 have also estimated the heritability of TS to be around 60%<sup>17</sup>. Our estimates suggest that  
260 TS/CTD may be even more heritable than previously thought.

261         Although we cannot conclusively rule out shared environmental factors, these appear  
262 to make a much smaller contribution to the etiology of the disorder. Instead, unique or  
263 non-shared environmental influences may confer increased risk to developing TS/CTD. A range  
264 of environmental risk factors for TS/CTD has been tentatively identified, including older  
265 paternal age and a number of peri-natal adversities (e.g., severe maternal stress, severe nausea  
266 and vomiting, smoking during the pregnancy as well as low birth weight and delivery  
267 complications low Apgar scores at birth) <sup>26-28</sup>. However, longitudinal, genetically informed  
268 studies are still rare; such studies should be prioritized alongside gene-searching efforts. The  
269 identification of genetic differences in susceptibility to particular environments (gene by  
270 environment interactions) in TS/CTD will be an important challenge for the future. Finally, the  
271 possibility of gene-environment correlations should also be investigated, as it is plausible that  
272 genetic factors could influence the specific environmental experiences of children vulnerable to  
273 developing TS/CTD <sup>29</sup>.



274           While chronic tic disorders are clearly more prevalent in males, both in clinical and  
275 epidemiological samples<sup>8-10,12,30</sup>, our results suggest that the familial risk for TS/CTD is  
276 comparable in male and female probands, regardless of the sex of the relative. The implication  
277 for molecular genetic research would be that when specific genes associated with TS/CTD are  
278 identified, they will be associated with TS/CTD in both sexes and that they will have similar  
279 effect sizes in males and females. However, these findings do not preclude the role of  
280 gender-specific factors during embryonic and fetal development in the causation of the disorder  
281<sup>31,32</sup>. Female sex may be a protective factor against TS/CTD; whether females require a greater  
282 familial etiologic load to manifest the phenotype, as has been suggested in Autism Spectrum  
283 Disorder<sup>33</sup>, is an interesting question for the future.

284

#### 285 *Strengths and limitations*

286 Strengths of the present study include the large population-based sample of TS/CTD cases  
287 diagnosed in Sweden over 40 years, all their relatives, as well as carefully matched, randomly  
288 selected controls. This ensured minimal risk of selection, recall, and report biases for both  
289 TS/CTD and control families. Further, this is the first study to have sufficient power to examine  
290 the familial risk of TS/CTD across relatives at varying genetic and environmental distances from  
291 the probands. Another important strength was careful selection of probands based on our

292 validation of the ICD codes in the Swedish National Patient Register, which resulted in an  
293 algorithm designed to minimize the risk of false positive diagnoses.

294         Registers also have limitations. Individuals diagnosed with TS/CTD in the National  
295 Patient Register probably represent only a fraction of all cases in the Swedish population. Many  
296 individuals with mild tics may not seek help and, thus, may never be diagnosed or treated.  
297 Furthermore, the National Patient Register only includes patients seen by specialist physicians  
298 (e.g. pediatricians, neurologists or psychiatrists); those diagnosed in primary care by general  
299 practitioners or other professionals (e.g. nurses) are not included. Finally, outpatients were only  
300 included in the register from 2001. Thus, the register may only include the more severe and  
301 complex forms of TS/CTD (in our cohort, over 70% of patients had at least one lifetime  
302 psychiatric comorbidity) and our results may not generalize to milder forms of the disorder.  
303 However, the incomplete coverage of TS/CTD cases in the Register should be constant across  
304 the families of probands and the families of comparison subjects, thus not influencing our  
305 estimates. It is theoretically possible that having a relative with TS/CTD increases the chance of  
306 seeking help/receiving a diagnosis, though our findings suggest small or negligible shared  
307 environmental effects, which would argue against this possibility. Another limitation is that  
308 longitudinal registers are subject to ‘left truncation’ or missing data before the date the register  
309 started, which may result in greater prevalence of TS/CTD in younger generations. However,  
310 since we matched for birth year and time at risk, such losses would be similar for both case and

311 control dyads and not affect family risks. Despite the very large sample size, our study could not  
312 distinguish between TS and CTD because our validation study suggested that clinicians in  
313 Sweden often use these diagnostic codes indistinctly. Finally, our results may not generalize to  
314 non-European populations; it has been suggested that ethnic differences in allelic frequencies  
315 may explain the low prevalence of TS/CTD in non-European populations <sup>10</sup>.

316

### 317 *Conclusions*

318 With these caveats in mind, our results indicate that TS/CTD is a strongly familial disorder  
319 within the Swedish population and the observed pattern of familiarity is consistent with a likely  
320 genetic etiology. Our heritability estimates place TS/CTD amongst the most heritable  
321 neuropsychiatric conditions.

322

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340

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436 **Table 1.** Risks of TS/CTD in relatives of probands diagnosed with TS/CTD in Sweden (1969-2009) compared with relatives of matched controls, and  
437 tetrachoric correlations.  
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Relation to proband	Average degree of genetic similarity	Number of dyads	Concordant pairs (expected)	Concordant pairs (observed)	Matched odds ratio (95% CI)	Tetrachoric correlation (Standard Error)
<b>First-degree relatives</b>						
Full siblings	50%	59,518	16.4	112	17.68 (12.90-24.23)	0.40 (0.01)
Parents	50%	95,675	3.2	24	21.08 (11.19-39.68)	0.30 (0.02)
Offspring	50%	16,572	3.1	24	24.74 (12.42-49.30)	0.30 (0.02)
<i>Total</i>	50%	171,765	22.8	160	18.69 (14.53-24.05)	
<b>Second-degree relatives</b>						
Maternal half-siblings	25%	15,767	5.2	16	4.41 (2.24-8.67)	0.22 (0.03)
Paternal half-siblings	25%	18,372	3.0	8	3.19 (1.27-8.00)	0.13 (0.04)
Uncles or aunts	25%	126,251	3.3	13	5.49 (3.04-9.89)	0.15 (0.03)
Nephews or nieces	25%	30,638	3.4	13	5.24 (2.83-9.72)	0.15 (0.03)
<i>Total</i>	25%	349,310	15.9	57	4.58 (3.22-6.52)	
<b>Third-degree relatives</b>						
First cousins	12.5%	238,822	21.8	56	3.07 (2.08-4.51)	0.11 (0.01)

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442 **Table 2.** Gender effects: Risks (OR, 95% Confidence Intervals and Tetrachoric correlations) for the presence of TS/CTD in relatives of probands  
443 diagnosed with TS/CTD.

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	Male-male pairs			Male-female pairs			Female-female pairs			Female-male pairs		
Relation to proband	Concordant pairs, observed	Matched OR (95% CI)	TC (SE)	Concordant pairs, observed	Matched OR (95% CI)	TC (SE)	Concordant pairs, observed	Matched OR (95% CI)	TC (SE)	Concordant pairs, observed	Matched OR (95% CI)	TC (SE)
First-degree relatives, total	84	16.75 (11.95-23.50)	0.34 (0.01 )	31	23.42 (13.26-41.38)	0.32 (0.02 )	14	17.48 (7.45-41.02 )	0.33 (0.03 )	31	21.65 (12.36-37.92)	0.32 (0.02 )
Second-degree relatives, total	35	4.78 (3.00-7.64)	0.12 (0.02 )	9	4.51 (2.29-8.90)	0.09 (0.03 )	4	5.53 (1.58-19.37 )	0.12 (0.04 )	9	3.86 (1.97-7.57)	0.09 (0.03 )
Third-degree relatives	32	2.69 (1.71-4.24)	0.11 (0.02 )	12	4.88 (2.60-9.18)	0.13 (0.03 )	0	-	-	12	4.29 (2.31-7.96)	0.13 (0.03 )

446 OR, Odds Ratios; CI, Confidence Interval; TC, Tetrachoric correlation; SE, Standard Error.

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450 **Table 3.** Model fitting results based on the family data.

<b>Models</b>	<b>-2 LL</b>	<b><math>\chi^2</math></b>	<b><math>\Delta</math> df</b>	<b><i>p</i>-value</b>	<b>AIC</b>	<b>Compared to</b>
I. ACE model with sex difference	142638.2				-30358610	
II. ACE model without sex difference	142642.5	4.3	2	0.12	-30358610	Model I
III. AE model without sex difference <sup>a</sup>	142642.6	0.1	1	0.70	-30358611	Model II

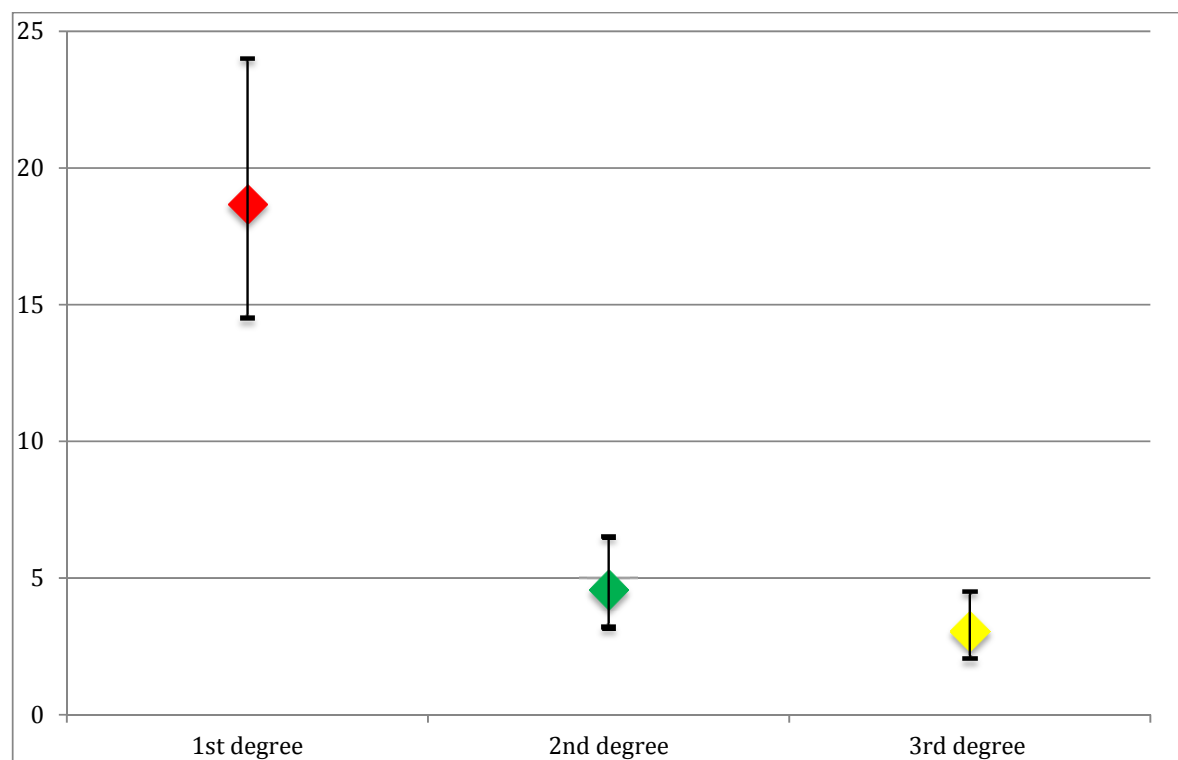
451

452 <sup>a</sup> Best fitting model.

453 Notes: - 2LL = minus twice the log likelihood;  $\chi^2$  = differences in -2LL statistic between submodel and full model;  $\Delta$  df = change in degrees of freedom

454 between submodel and full model; p=probability; AIC = Akaike Information Criterion.

**Figure 1.** Risks (OR and 95% CI) for TS/CTD among first, second and third degree relatives of TS/CTD probands in the Swedish National Patient Register (1969-2009) compared to matched population controls.



Legend: First-degree relatives included full siblings, parents, and children. Second-degree relatives included maternal and paternal half siblings, grandparents and grandchildren, uncles/aunts, and nephews/nieces. Third-degree relatives consisted of first cousins.